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Synthesis and antimicrobial evaluation of varied ring new heterocycles

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In the present study, a series of pyrazolines **2a-c**, isoxazoline **5**, pyrimidines **3a′-c′** and benzoazepines **4a′′-c′′** have been prepared from the cyclization reactions of biphenyl chalcone **1** with appropriate binucleophilic reagents. The chalcone **1** has been obtained by using the Claisen-Schmidt condensation reaction of 2-hydroxyacetophenone with biphenyl-4-carboxaldehyde in EtOH/NaOH medium. The structural interpretations of the chalcone **1** and final heterocycles have been fully ascribed on the basis of their different spectroscopic parameters such as IR, ^{1}H and ^{13}C NMR, and ESI-MS. The *in vitro* antimicrobial evaluation of these heterocycles have also been carried out by using serial tube dilution technique against the selected number of bacterial and fungal strains and most of the studied products proved to be the potent antimicrobial agents. The newly prepared pyrazolines and isoxazoline exhibit noticeable antimicrobial properties.

Keywords: Chalcone, pyrazoline, isoxazoline, pyrimidine, benzodiazepine, benzoxazepine, benzothiazepine, antimicrobial

Heterocyclic chemistry has been one of the significant branch of organic syntheses which has provided the useful thrust area to the synthetic as well as analytical chemists for rapid development in the different fields such as medicinal, analytical and pharmaceutical industries[1,2]. These compounds are challenging models for the diversity of bioactive products which are considered as the precursor vehicles for the preparations of the many chemically and biologically useful scaffolds[3]. The most of known products in the nature are heterocyclic in character and their numbers have been expanding continuously due to their versatile applications in the industrial as well as biological systems[4]. The nitrogen, sulfur and oxygen have been widely exploited as the hetero atoms in these compounds[5,6]. The significant aspect of heterocycles is their ability for incorporating the functional groups on their rings as the substituents. The modern day's development of research works in the field of synthetic chemistry have become the key challenge for the researchers in order to investigate novel and efficient protocols for the preparations of exotic heterocyclic system. Thus, these days major emphasis has been directed upon the designing, constructions and recognitions of the biologically promising new heterocycles[7-11].

The molecules bearing two completely delocalized aromatic rings joined through the α,β-unsaturated carbonyl group are named as chalcones that are widely identified as the significant building block in the synthesis of many biologically significant compounds, polymers as well as in potential drug target molecules[12-19]. Chalcones are the polyphenolic natural products that are found to be present in vegetables, fruits, spices, tea and soya based foodstuffs[20,21]. Recently, molecular docking studies have revealed that chalcone derivatives are also being utilized as the potential epidermal growth factor receptor inhibitors[22-25].

Pyrazoles are the most privileged five membered heterocyclic scaffolds having two nitrogen atoms at adjoining locations in the ring and their partially reduced structures are named as pyrazolines[26-28]. The immense applications of this moiety in the biological field have increased the enormous curiosity among the chemists to investigate their structural frame work[29,30]. The pyrazole moiety has been found to exist in various well-established pharmaceutical drugs such as lonazolac **1** (anti-inflammatory), rimonabant **2** (anti-obesity), difenamizole **3** (analgesic), CDPPB **4** (antipsychotic) and betazole **5** (H_2-receptor agonist)[31-35] (Figure 1). The existence of this scaffold in many bioactive products and broad spectrum of chemotherapeutic products have led to their great role in different areas like medicine, agriculture and technology[36]. Pyrazoles and their derivatives have been utilized as the antimicrobial[37], anticancer[38], anti-tubercular[39], anticonvulsant[40], antioxidants[41], anti-depressants[42] and antiviral agents[43].

Isoxazoles are the decisive set of five membered heterocycles in which oxygen and nitrogen are situated at the contiguous positions whereas their dihydro forms are described as isoxazolines[44-46]. These substrates have acquired considerable importance due to their valuable agrochemical and pharmacological properties[47-53]. Isoxazole moiety is also found to be present in some of the indispensable drugs like leflunomide **6**, sulfafurazole **7**, valdecoxib **8** and oxacillin **9**[54,55] (Figure 2). Isoxathion, isouron and isoxaben are the examples of degradable pesticides containing substituted isoxazoles in their structural skeleton[56,57].

Pyrimidines are belonging to diazines family containing two nitrogen atoms at 1,3-positions in the six membered aromatic rings[58]. The synthetic studies of these heterocycles have been extensively exploited owing to their presence in a large variety of drugs, co-enzymes, natural products, nucleic acids and vitamins[59-68]. The top marketing pharmaceutical products such as zidovudine **10**, floxuridine **11**, minoxidil **12**, pyrimethamine **13**, flucytosine **14**, lamivudine **15** and lopinavir **16** are consisting of pyrimidine ring systems[69] (Figure 3). This heterocycle is also found to be present in some useful derivatives of barbituric acid like pentothal, veronal and luminal which are used as the potential therapeutic agents[70-73].

The studies of seven membered heterocycles azepines and their polycyclic derivatives have attracted much attention in the past decades due to their wide spectrum of industrial and biological significances[74,75]. 1,2-Oxazepines and 1,2-diazepines are known to act as the potential opioid analgesics and antihypertensive agent respectively[76,77]. The diazepam **17** have been used as the antianxiety drug and quazepam **18** as anticonvulsant[78] (Figure 4). 1,5-Benzothiazepines are found to be related with vasodilator, Ca-antagonist and platelet aggregation inhibitor actions[79].

Presently in the field of synthetic and medicinal chemistry, the foremost point is to investigate the synthesis of novel heterocyclics with promising bioactivities. Therefore, these days major researches have been directed upon the development of proficient methods to obtain the potential heterocyclic products with privileged structures[80-83].

The presence of two electrophilic reactive centers in the structural unit of chalcone makes them highly versatile and attractive synthons for the preparations of the variety of biologically potent varied ring

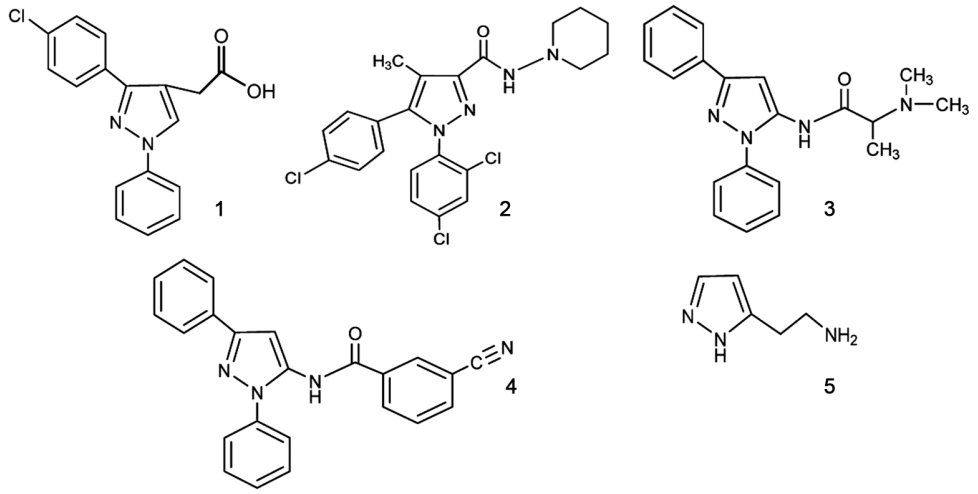


Figure 1

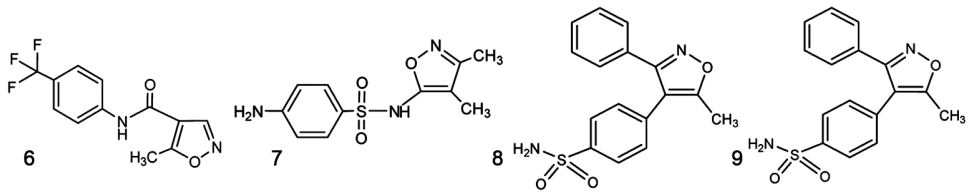


Figure 2

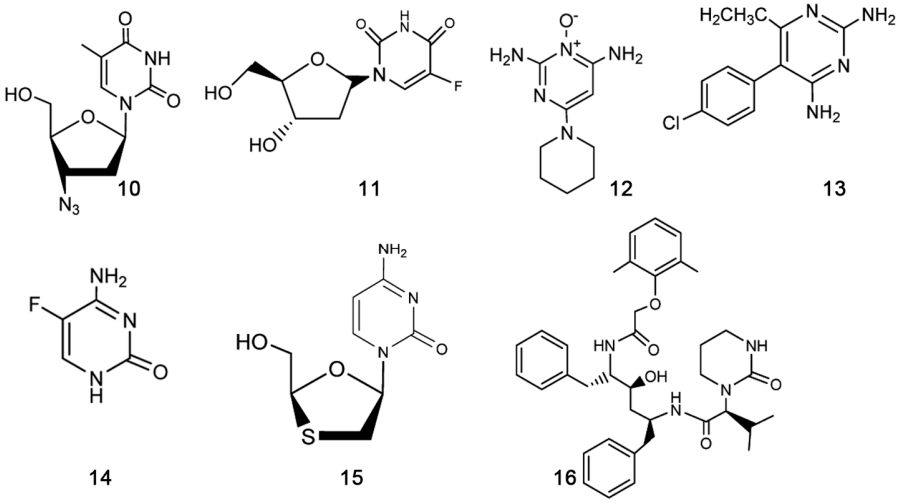


Figure 3

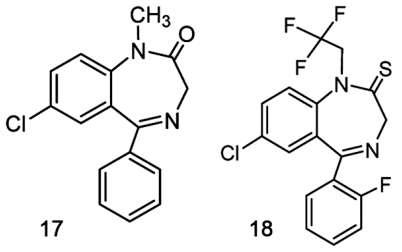


Figure 4

heterocycles systems (five/six/seven membered) through their cyclization reactions with suitable bi-nucleophilic reagents[84-89].

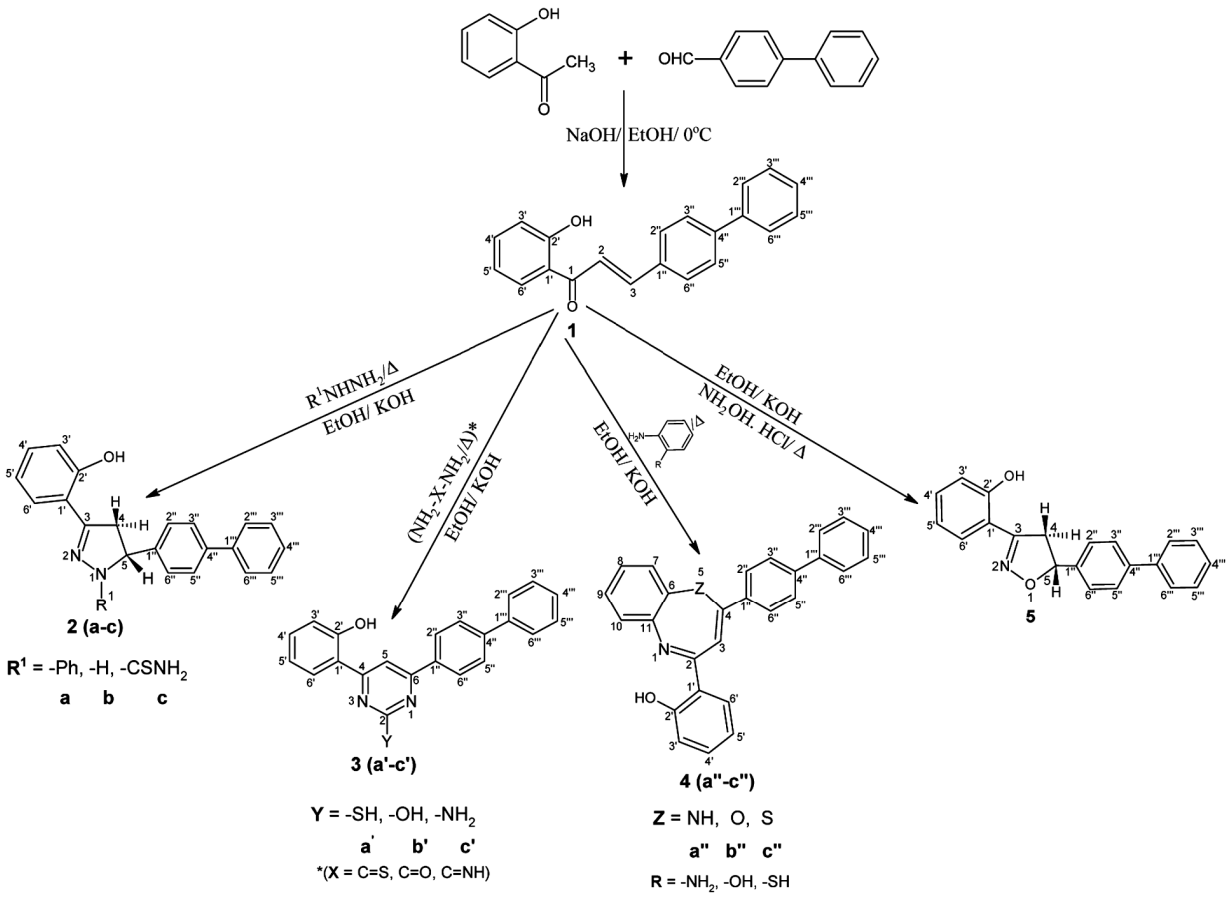
Encouraged by the above literature studies and on the basis of our preceding efforts on synthesis of new heterocyclic products[90-94], the proposed researches have been focused upon the chemical transformations of chalcone **1** with variety of binucleophilic reagents in order to acquire new pyrazoline, isoxazoline, pyrimidine, benzodiazepine, benzoxazepine and benzothiazepine derivatives. The main interest behind the preparations of these heterocycles was to explore the effect of the ring size of heterocyclic moiety (five/six/seven membered) upon their formations and the antimicrobial properties.

Results and Discussion

The heterocycles **2(a-c)**, **3(a′-c′)**, **4(a″-c″)** and **5** have been prepared conveniently in the laboratory by using the cyclocondensation reactions of biphenyl chalcone **1** with appropriate ring closure reagents (phenyl hydrazine, hydrazine hydrate, thiosemicarbazide, hydroxylamine hydrochloride, thiourea, urea, guanidine hydrochloride, *o*-phenylenediamine, 2-aminophenol and 2-aminothiophenol) under the refluxing conditions. The chalcone **1** was attained from the Claisen-Schmidt condensation reaction of 2-hydroxyacetophenone and biphenyl-4-carboxaldehyde in EtOH/NaOH medium. The structures of the chalcone **1** and final heterocycles have been completely attributed on the account of their various spectroscopic strategies (IR, ^{1}H NMR, ^{13}C NMR, and ESI-MS) and the purity of these products was assured from their TLC and elemental analysis results. The pathway for the synthesis of chalcone **1** and target compounds **2(a-c)**, **3(a′-c′)**, **4(a″-c″)** and **5** have been outlined in Scheme I.

IR spectrum of chalcone **1** demonstrated the three apparent bands at 3372 (O-H), 1652 (C=O) and 1574 cm^{-1} (C=C). In its ^{1}H NMR spectrum (400 MHz, DMSO-d_6), the emergence of D_2O exchangeable broad singlet positioned at δ 9.68 defines the presence of the O*H* group proton. The double bond hydrogens H-3 and H-2 were found to be resonating in the form of a doublet each at δ 7.81 and 7.76 respectively and the coupling value of $J_{2,3}$=15.6 Hz established their *trans* correlation. The thirteen protons belonging to C_1-phenyl (H-3′, 4′, 5′, 6′) and C_3-biphenyl rings (H-2″, 3″, 5″, 6″, H-2‴, 3‴, 4‴, 5‴, 6‴) revealed the signals in the aromatic region at the appropriate places (*vide* Experimental Section).

^{13}C NMR spectrum (100 MHz, DMSO-d_6) was further very supportive for illustrating its carbon scaffold. The appearance of most downfield resonance at δ 189.03 may be ascribed to the carbonyl



Scheme I — Synthesis of pyrazolines **2a-c**, pyrimidines **3a′-c′**, benzoazepines **4a″-c″** and isoxazoline **5**

group whereas carbon atoms of the olefinic bond C-3 and C-2 exhibited their suitable signals at δ 143.18 and 119.26 respectively. The other perceptible signal was displayed by the C-2′ carbon at δ 157.68 due to its direct connection with oxygen atom of the hydroxyl group. The remaining aromatic carbon atoms related to C_1-phenyl and C_3-biphenyl rings were found to be positioned at the expected δ values (*vide* Experimental Section).

IR spectra of heterocycles **2(a-c), 3(a′-c′), 4(a″-c″)** and **5** showed the broad bands at 3500-3214 cm^{-1} which ascribed the presence of O-H functional group in their structures. The existence of O*H* substituent in these compounds was again corroborated from their ^{1}H NMR spectra (400 MHz, C*D*Cl$_3$/ DMSO-d_6) by the manifestation of D_2O exchangeable broad singlets at δ 9.86-7.27.

IR spectra of **2(a-c)** showed the substantial absorptions at 1596-1590 cm^{-1} owing to the C=N stretching frequency of the pyrazoline ring. The appearance of intense absorption at 3458 cm^{-1} suggested the presence of N-H group in compound **2b**. Product **2c** exhibited three noticeable bands at 3447, 3419 (N-H) and 1199 (C=S) cm^{-1}. In the ^{1}H NMR (400 MHz, CDCl$_3$/DMSO-d_6) spectra of pyrazolines **2(a-c),** the imperative aspect was the three well distinctive doublet of doublets situated at δ 6.00-5.28, 3.97-3.80 and 3.15-3.12 that could be easily attributed to pyrazoline ring protons Hx, H_M and H_A respectively. The presence of chiral center at C-5 carbon of the pyrazoline ring is found to be responsible for the AMX splitting pattern of these three protons and the stereochemical interactions among these protons was elucidated on the basis of their mutual coupling constants. The coupling value of J_{XA}=6.9-3.3 Hz represent the *trans* disposition of H_X and H_A whereas J_{XM}=12.1-11.5 Hz depicts the *cis* orientation of H_X and H_M with respect to each other. The coupling constant of J_{MA}=18.0-17.2 Hz proves that H_M and H_A are geminally placed at C-4. In compound **2c**, the presence of two broad singlets integrating for one hydrogen each at δ 8.12 and 7.93

correspond to the two NH_2 group protons. The occurrence of broad singlet at δ 8.99 was easily assignable to N*H* group proton in compound **2b**. The C_3-phenyl and C_5-biphenyl rings protons produced their appropriate signals in the aromatic region (*vide* Experimental Section).^{13}C NMR (100 MHz, DMSO-d_6) spectra of **2(a-c)** were quite influential to authenticate their carbon framework which displayed noticeable signals at δ 158.31-157.46 due to C-2″ in **2a** and C-2′ in **2b** and **2c**. The appearance of three appropriate resonances centered at δ 155.15-147.31 (C-3), 63.23-62.54 (C-5) and 42.94-42.38 (C-4) confirmed the formation of pyrazoline rings. The location of downfield signal at δ 175.99 was able to validate the presence of C=S group in product **2c**. The remaining aromatic rings carbon atoms (C_3-phenyl and C_5-biphenyl) were found to be located at the appropriate δ values (*vide* Experimental Section).

IR spectra of pyrimidines **3(a′-c′)** showed the major absorptions at 3379, 3305 (N-H), 3378 (O-H) and 2644 cm^{-1} (S-H). The absence of C=O functional group band represented its involvement in the chemical transformations and here noticeable absorptions were observed at 1597-1590 cm^{-1} due to the C=N moiety of the diazine ring. ^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6) spectra of **3(a′-c′)** showed the characteristic signals in the form of appropriate singlet at δ 8.38-7.65 that could be easily assigned to the H-5 of pyrimidine ring along with D_2O exchangeable resonances of C_2-NH_2, C_2-S*H* and C_2-O*H* group protons at δ 8.40, 13.68 and 9.83 respectively. The remaining aromatic ring protons (C_4-phenyl and C_6-biphenyl) were centered at the suitable δ values (*vide* Experimental Section). ^{13}C NMR (100MHz, DMSO-d_6) spectra of **3(a′-c′)** exhibited the resonances of pyrimidine ring carbon atoms at δ 178.60-165.18 (C-2), 165.76-163.41 (C-4), 163.18-160.96 (C-6) and 109.98-106.96 (C-5). The C_4-phenyl and C_6-biphenyl rings carbon atoms were situated in the aromatic regions at the appropriate δ values (*vide* Experimental Section).

IR spectra of seven membered heterocycles **4(a″-c″)**, showed the intense band at 1600-1589 cm^{-1} that suggested the presence of C=N group in their structures. The appearance of perceptible absorption at 3480 cm^{-1} affirmed the presence of *N-H* group in benzodiazepine **4a″**. In the ^{1}H NMR spectra (400 MHz, $CDCl_3$/DMSO-d_6) of **4a″**, presence of N*H* proton was further established from the appearance of a broad singlet at δ 8.71. The formation of the heterocycles **4(a″-c″)** were confirmed from the appearance of suitable singlets at δ 6.33-5.25 which may be resulted by the H-3 proton of the seven membered ring. The remaining hydrogens were found to be resonating in the aromatic region at the suitable δ values (*vide* Experimental Section). In the ^{13}C NMR (100 MHz, DMSO-d_6) spectra of **4(a″-c″),** the heterocyclic ring five carbon atoms C-2, C-6, C-11, C-4 and C-3 were easily resonating at δ 164.68-164.15, 152.43-150.01, 145.08-143.35, 143.88-142.17 and 99.15-90.37 respectively. The carbon atoms of the aromatic rings (C_2-phenyl and C_4-biphenyl) produced their signals at their appropriate places (*vide* Experimental Section).

In the IR spectrum of of isoxazoline **5,** a band was observed at 1600 cm^{-1} that proved the existence of C=N moiety in this molecule. Its ^{1}H NMR spectrum (400 MHz, $CDCl_3$) was very accessible to elucidate its structure. Three well splitted doublet of doublets situated at δ 5.62, 3.75 and 3.18 were easily allocated to isoxazoline ring protons H_X, H_M and H_A respectively that corroborated the presence of AMX splitting system in isoxazoline. The coupling values confirmed the stereochemical correlation among these hydrogens. The vicinal coupling value of 11.5 Hz between the H_X and H_M revealed their *cis* relationship while coupling constant of 4.6 Hz between H_X and H_A suggested the *trans* association between these protons. The coupling value of 17.2 Hz demonstrated the *geminal* location of H_A and H_M at C-4. Rest of the protons belonging to C_3-phenyl and C_5-biphenyl rings could generate their suitable signals in the aromatic region (*vide* Experimental Section). In the ^{13}C NMR (100 MHz, DMSO-d_6), the isoxazolidine ring carbon atoms C-3, C-5 and C-4 furnished their appropriate signals at δ 154.25, 60.13 and 42.05 respectively. The recognizable signals present at δ 157.52 confirmed the presence of C-2′ because of its direct bonding with oxygen atom. The C_3-phenyl and C_5-biphenyl ring carbon atoms were found to be situated in the aromatic regions (*vide* Experimental Section).

The structural features of the newly prepared heterocycles **2(a-c)**, **3(a′-c′)**, **4(a″-c″)** and **5** were further corroborated on the basis of their ESI-MS spectral data (*vide* Experimental Section).

Antimicrobial Activity of 2(a-c), 3(a′-c′), 4(a″-c″) and 5

The *in vitro* antimicrobial assessment of all the newly synthesized heterocycles **2(a-c), 3(a′-c′), 4(a″-c″)** and **5** was implemented with the help of serial

tube dilution process[95] against the seven bacterial (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klubsellia pneumonia*, *Bacillius subtilis*, *Staphylococcus aureus*, *Pseudomonas fluorescens and Streptoccus pyrogens)* and five Fungal pathogens (*Aspergillus sclerotum*, *Aspergillus janus*, *Penicillium glabrum*, *Aspergillus niger* and *Fusarium oxysporum).* The MIC estimations of these heterocycles against the above depicted microorganisms was carried out by making varied concentrations of 128, 64, 32, 16, 8 and 4 µg/mL in DMSO that was served in the form of negative control. The smallest concentration of the heterocycles essential to suppress the noticeable production of a microorganism after incubation was measured as the minimum inhibitory concentration. Standard antimicrobial drugs such as *Amoxicillin* (for antibacterial) and *Fluconazole* (for antifungal) were used to contrast the MIC outcome of all the tested products. These drugs provided as the positive control. Nutrient broth and malt extract medium supplied as the nourishment to bacteria and fungi respectively. The accessibility of the concerned compounds on the microbial growth was viewed from the emergence of turbidity within the test tubes after 24 h of incubation at 37°C for bacterial cultures and 72 h of incubation at 28°C for fungal species. The minimum inhibitory concentration (MIC) results of **2(a-c), 3(a′-c′), 4(a″-c″)** and **5** have been expressed in Table I.

It is apparent from Table I that heterocycle **2a** provided potent behaviours against *E. coli*, *S. aureus* and *F. oxysporum* at the MIC of 8 µg/mL whereas compound **2b** was found to be highly active (MIC-8 µg/mL) against *K. pneumonia*, *A. janus* and *A. sclerotiorum.* The products **2c** suppressed the growth of *P. fluorescens*, *S. pyogenes*, *F. oxysporum* at the MIC of 8 µg/mL. The compound **5** could afford appreciable activity (MIC-8 µg/mL) against *S. aureus*, *P. glabrum* and *A. niger*. Product **3a′** exhibited MIC of 8 µg/mL against *P. Aeruginosa.* The heterocycles **3b′** and **3c′** demonstrated recognizable results against *E. coli*, *A. janus*, *K. pneumonia* and *S. pyogenes* respectively at the MIC of 8 µg/mL. Compounds **4a″** and **4b″** showed effectual response against *P. fluorescens* and *P. aeruginosa* respectively at the similar MIC values whereas product **4c″** attained moderate inhibitory activitiy against *P. fluorescens* and *F. oxysporum.*

It is also comprehensible from these results that majority of the prepared heterocycles revealed modest level of actions against the tested microorganisms (MIC-16 µg/mL).

The above given antimicrobial results emphasized that pyrazolines **2(a-c)** and isoxazoline **5** exhibited promising antibacterial and antifungal properties as compared to pyrimidine **3(a′-c′)** and benzoazepine **4(a″-c″)** derivatives.

Experimental Section

Materials and methods

The entire reagents and solvents needed for the present investigations were procured from E-Merck, S. D. Fine-Chem. Limited, Sigma-Aldrich Corporations and open capillary tube equipment was used for evaluating the melting points of the newly prepared heterocycles. TLC plates coated with Silica-Gel G were utilized to scrutinize the progress of given reactions and purity of products was assessed by taking the hexane and ethyl acetate (1:1) as the mobile

Table I — *In vitro* MIC (µg/mL) data of **2a-c**, **3a′-c′**, **4a″-c″** and **5**

Compd	Gram (-ve) bacteria				Gram (+ve) bacteria			Fungi				
	E. coli	*K. pneumonia*	*P. Aeruginosa*	*P. Fluorescens*	*S. aureus*	*B. subtilis*	*S. Pyogenes*	*A. Janus*	*P. Glabrum*	*A. Niger*	*F. oxysporum*	*A. sclerotiorum*
2a	8	32	16	32	8	32	16	32	32	32	8	32
2b	16	8	32	16	32	16	32	8	16	16	32	8
2c	32	16	32	8	32	32	8	16	32	32	8	16
3a′	32	32	8	32	16	32	32	32	16	32	32	16
3b′	8	32	32	16	32	32	32	8	32	32	16	32
3c′	32	8	32	32	32	32	8	32	16	32	32	32
4a″	32	32	32	8	32	32	32	32	32	32	16	32
4b″	32	32	8	32	32	32	16	32	32	16	32	32
4c″	32	32	32	16	32	32	32	32	32	32	16	32
5	32	16	16	32	8	32	16	32	8	8	32	16
Amoxicillin	4	4	4	4	2	2	4	–	–	–	–	–
Fluconazole	–	–	–	–	–	–	–	2	2	2	2	2

phase and spots were observed by placing these plates in the iodine chamber. Perkin XEVO G2-XS QTOF and Elmer FT-IR spectrophotometers have been employed for recording the ESI-MS and Infrared spectra respectively. ^{1}H and ^{13}C NMR spectra were scanned on Bruker Advance-II Spectrometer operating at 400 MHz and 100 MHz respectively by taking suitable deuterated solvents (DMSO-d_6/C*D*Cl$_3$) as well as tetramethylsilane (TMS) in the form of internal standard and chemical shifts are reported in δ (ppm) values.

Synthesis of (2*E*)-3-(biphenyl-4-yl)-1-(2-hydroxy phenyl)prop-2-en-1-one, 1

A mixture of 2-hydroxyacetophenone (3.0 g, 0.022 mol), bipheny-4-carboxaldehyde (4.0 g, 0.022 mol), dry ethanol (25.0 mL) and sodium hydroxide (3.5 g, 0.087 mol) was intensely stirred at 0ºC for 5 h on a magnetic stirrer. Upon the execution of the reaction, the mixture was transformed into a reddish mass that was covered and placed in a refrigerator for 12 h. After that the resulting reaction mixture was poured slowly into the crushed ice with constant shaking and its neutralization was carried out with dilute HCl to furnish a light yellow solid which was crystallized by taking the equimolar quantity of MeOH:CHCl$_3$ to realize a pure compound **1**.

1: Yield 5.5 g (85%), light yellow needles, m.p. 142-144°C. IR (KBr): 3372 (O-H), 3030 (aromatic C-H), 1652 (C=O), 1574 (C=C) and 1558, 1519, 1486, 1451 cm^{-1} (aromatic C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.68 (1H, brs, O*H*), 7.90 (2H, d, J_o = 8.3 Hz, H-2″, 6″), 7.81 (1H, d, J_{trans} = 15.6 Hz, H-3), 7.76 (1H, d, J_{trans} = 15.6 Hz, H-2), 7.71 (4H, m, H-3″, 5″, 2‴, 6‴), 7.59 (1H, d, J_o = 7.8 Hz, H-6′), 7.46 (3H, m, H-3‴, 4‴, 5‴), 7.39 (1H, d, J_o = 7.8 Hz, H-5′), 7.34 (1H, d, J_o = 7.1 Hz, H-3′), 7.04 (1H, dd, $J_{m,o}$ = 2.5, 8.0 Hz, H-4′)); ^{13}C NMR (100 MHz, DMSO-d_6): δ 189.03 (C=O), 157.68 (C-2′), 143.18 (C-3), 142.17 (C-1″), 139.28 (C-1′), 139.02 (C-4″), 133.60 (C-1‴), 129.43 (C-2″, 6″), 129.05 (C-3″, 5″), 128.72 (C-2‴, 6‴), 127.67 (C-3‴, 5‴), 126.97 (C-4‴), 126.53 (C-6′), 121.86 (C-5′), 120.06 (C-3′), 119.26 (C-2), 114.68 (C-4′); ESI-MS: *m/z* 301 (M+1, 100%), 300 (M$^+$, 20%). Anal. Calcd for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 84.31; H, 5.39%.

Synthesis of (*R*)-2-(5-[1,1′-biphenyl]-4-yl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)phenol, 2a

A suspension of chalcone **1** (1.0 g, 0.003 mol), phenyl hydrazine (0.4 g, 0.003 mol), KOH (0.3 g, 0.006 mol) and dry EtOH (25.0 mL) was heated under reflux for 6 h. The accomplishment of reaction was analyzed with the help of TLC [hexane:ethyl acetate (9:1)]. The mixture was cooled at room temperature and solvent was evaporated under reduced pressure. The resulting mass was added gently into ice cold hydrochloric acid solution to afford the crude product which was filtered off, dried and recrystallized from methanol to obtain the pure pyrazoline **2a**.

2a: Yield 0.95 g (73%), light brown solid, m.p. 148-150°C. IR (KBr): 3500 (O-H), 3077 (aromatic C-H), 2928 (aliphatic C-H) and 1596 cm^{-1} (C=N); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.54 (4H, d, J_o = 7.2 Hz, H-3‴, 5‴, 2⁗, 6⁗), 7.41 (2H, t, J_o = 7.3 Hz, H-5″, 6″), 7.36 (2H, d, J_o = 8.1 Hz, H-3⁗, 5⁗), 7.31 (2H, d, J_o = 7.2 Hz H-2‴, 6‴), 7.27 (1H, brs, O*H*), 7.18 (4H, m, H-3′, 4′, 5′, 4⁗), 7.09 (2H, d, J_o = 7.9 Hz, H-3″, 4″), 6.80 (2H, d, J_o = 7.0 Hz H-2′, 6′), 5.28 (1H, dd, J_{XA} = 6.9 Hz, J_{XM} = 11.6 Hz, H$_X$), 3.80 (1H, dd, J_{MX} = 11.6 Hz, J_{MA} = 17.2 Hz, H$_M$), 3.12 (1H, dd, J_{AX} = 6.9 Hz, J_{AM} = 17.2 Hz, H$_A$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.46 (C-2″), 147.31 (C-3), 144.19 (C-1′), 141.64 (C-1‴), 139.64 (C-4‴), 139.25(C-1⁗), 133.47 (C-1″), 129.70 (C-2‴, 6‴), 128.91 (C-3‴, 5‴), 128.88 (C-2⁗, 6⁗), 127.41 (C-3⁗, 5⁗), 127.29 (C-3′, 5′), 126.56 (C-5″), 126.47 (C-4⁗), 118.57 (C-4′), 116.90 (C-6″), 116.05 (C-2′, 6′), 112.89 (C-4″), 111.98 (C-3″), 62.71 (C-5), 42.94 (C-4); ESI-MS: *m/z* 392 (M+2, 27%), 391 (M+1, 100%). Anal. Calcd for $C_{27}H_{22}N_2O$: C, 83.05; H, 5.68; N, 7.17. Found: C, 83.38; H, 5.70; N, 7.20%.

Synthesis of (*R*)-2-(5-[1,1′-biphenyl]-4-yl)-4,5-dihydro-1*H*-pyrazol-3-yl)phenol, 2b

The reaction of compound **1** (1.0 g, 0.003 mol) with hydrazine hydrate (0.2 g, 0.003 mol) in the same way as illustrated above for **2a** led to the generation of heterocyclic **2b**.

2b: Yield 0.75 g (75%), Off white solid, m.p. 144-146°C. IR (KBr): 3458 (N-H), 3264 (O-H), 3054 (aromatic C-H), 2920 (aliphatic C-H) and 1592 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.48 (1H, brs, O*H*), 8.99 (1H, brs, N*H*), 7.69 (4H, t, J_o = 7.7 Hz, H□2‴, 3‴, 5‴, 6‴), 7.47 (2H, t, J_o = 7.1 Hz, H-2″, 6″), 7.41 (1H, t, J_o = 7.5 Hz, H-4⁗), 7.34 (2H, m, H-3″, 5″), 7.25 (3H, t, J_o = 8.0 Hz, H-4′, 5′, 6′), 6.94 (1H, dd, $J_{m,o}$ = 2.1, 8.1 Hz, H-3′), 5.62 (1H, dd, J_{XA} = 6.1 Hz, J_{XM} = 12.1 Hz, H-X), 3.87 (1H, dd, J_{MX} = 12.1 Hz, J_{MA} = 17.9 Hz, H-M), 3.13 (1H, dd, J_{AX} = 6.1 Hz, J_{AM} = 17.9 Hz, H-A); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.31 (C-2′), 154.26 (C-3), 143.20 (C-1″), 140.64

(C-4″), 138.44 (C-1‴), 133.01 (C-1′), 130.87 (C-2″, 6″), 128.24 (C-3″, 5″), 127.55 (C-4‴)126.28 (C-2‴, 6‴), 126.08 (C-3‴, 5‴), 124.79 (C-5′), 118.23 (C-6′), 116.77 (C-4′), 112.81 (C-3′), 63.23 (C-5), 42.62 (C-4); ESI-MS: *m/z* 337 (M+Na, 65%), 316 (M+2, 32%), 315 (M+1, 15%). Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.55; H, 5.79; N, 8.87%.

Synthesis of (*R*)-5-([1,1′-biphenyl]-4-yl)-3-(2-hydroxyphenyl)- 4,5-dihydro-1*H*-pyrazole-1-carbothioamide 2c

The product **2c** was prepared by treating **1** (1.0 g, 0.003 mol) with thiosemicarbazide (0.2 g, 0.003 mol) using the similar protocol as suggested previously for **2a**.

2c: Yield 0.83 g (69%), light yellow solid, m.p. 218-220°C. IR (KBr): 3447, 3419 (N-H), 3291 (O-H), 3050 (aromatic C-H), 2924 (aliphatic C-H), 1590 (C=N) and 1199 cm^{-1} (C=S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.72 (1H, brs, O*H*), 8.12 (1H, brs, NH_α), 7.93 (1H, brs, NH_β), 7.68 (4H, t, J_o = 8.1 Hz, H-2‴, 3‴, 5‴, 6‴), 7.49 (2H, t, J_o = 7.4 Hz, H-2″, 6″), 7.38 (1H, t, J_o = 7.3 Hz, H-4‴), 7.32 (2H, m, H-3″, 5″), 7.28 (3H, t, J_o = 8.7 Hz, H-4′, 5′, 6′), 6.94 (1H, dd, $J_{m,o}$ = 1.8, 8.7 Hz, H-3′), 6.00 (1H, dd, J_{XA} = 3.3 Hz, J_{XM} = 11.5 Hz, H-X), 3.97 (1H, dd, J_{MX} = 11.5 Hz, J_{MA} = 18.0 Hz, H-M), 3.15 (1H, dd, J_{AX} =3.3 Hz, J_{AM} = 18.0 Hz, H-A); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.99 (C=S), 157.48 (C-2′), 155.15 (C-3), 142.15 (C-1″), 139.87 (C-4″), 138.85 (C-1‴), 132.09 (C-1′), 129.71 (C-2″, 6″), 128.90 (C-3″, 5″), 127.33 (C-4‴)126.87 (C-2‴, 6‴), 126.55 (C-3‴, 5‴), 125.92 (C-5′), 118.14 (C-6′), 117.71 (C-4′), 113.58 (C-3′), 62.54 (C-5), 42.38 (C-4); ESI-MS: *m/z* 374 (M+1, 25%), 373 (M^+, 100%). Anal. Calcd for $C_{22}H_{19}N_3OS$: C, 70.75; H, 5.13; N, 11.25; S, 8.58. Found: C, 70.46; H, 5.15; N, 11.29; S, 8.61%.

Synthesis of 2-(6-([1,1′-biphenyl]-4-yl)-2-mercaptopyrimidin-4-yl)phenol 3a′

A mixture of compound **1** (1.0 g, 0.003 mol), thiourea (0.3 g, 0.003 mol) and KOH (0.3 g, 0.006 mol) was dissolved in EtOH (25.0 mL) and allowed to reflux for 5 h. After the accomplishment of reaction (as examined through TLC), the entire mixture was poured on to crushed ice with continuous shaking to achieve a yellow substance which was filtered under suction, washed successively with water and dried. The resulting crude product was purified from its crystallization in MeOH to provide a pure product **3a′**.

3a′: Yield 0.8 g (67%), yellow solid, m.p. 94-96°C. IR (KBr): 3408 (O-H), 3027 (aromatic C-H), 2644 (S-*H*) and 1590 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.68 (1H, brs, S-*H*), 9.86 (1H, brs, O-*H*), 8.38 (1H, s, H-5), 7.88 (2H, d, J_o = 8.0 Hz, H-2″, 6″), 7.74 (4H, m, H-3″, 5″, 2‴, 6‴), 7.41 (6H, m, H-4′, 5′, 6′, 3‴, 4‴, 5‴), 6.98 (1H, dd, $J_{m,o}$ = 2.5, 7.2 Hz, H-3′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.60 (C-2), 165.76 (C-4), 163.18 (C-6), 157.68 (C-2′), 143.51 (C-1″), 138.81 (C-4″, 1‴), 129.94 (C-1′), 129.08 (C-2″, 6″), 128.93 (C-3″, 5″), 128.31 (C-2‴, 6‴), 127.98 (C-3‴, 5‴), 126.94 (C-5′), 126.90 (C-4‴), 126.74 (C-6′), 119.08 (C-4′), 114.74 (C-3′), 109.98 (C-5); ESI-MS: *m/z* 379 (M+Na, 49%), 357 (M+1, 63%), 356 (M^+, 100%). Anal. Calcd for $C_{22}H_{16}N_2OS$: C, 74.13; H, 4.52; N, 7.86; S, 8.99. Found: C, 73.83; H, 4.54; N, 7.89; S, 8.95%.

Synthesis of 4-([1,1′-biphenyl]-4-yl)-6-(2-hydroxyphenyl)pyrimidin-2-ol, 3b′

The compund **3b′** was realized from the reaction of **1** (1.0 g, 0.003 mol) with urea (0.2 g, 0.003 mol) by succeeding the usual method as affirmed formerly for **3a′**.

3b′: Yield 0.8 g (72%), yellow solid, m.p. 122-124°C. IR (KBr): 3402 (C_2′-OH), 3378 (C_2-OH), 3038 (aromatic C-H) and 1597 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.04 (1H, brs, C_2′-O*H*), 9.83 (1H, brs, C_2-O*H*), 7.91 (2H, d, J_o = 7.3 Hz, H-2″, 6″), 7.71 (4H, m, H-3″, 5″, 2‴, 6‴), 7.65 (1H, s, H-5), 7.48 (3H, m, H-3‴, 4‴, 5‴), 7.42 (1H, d, J_o = 7.9 Hz, H-5′), 7.31 (1H, dd, $J_{m,o}$ = 2.3, 7.0 Hz, H-6′), 7.01 (2H, d, J_o = 7.3 Hz, H-3′, 4′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.59 (C-2), 163.41 (C-4), 160.95 (C-6), 158.47 (C-2′), 145.32 (C-1″), 139.27 (C-4″, 1‴), 130.21 (C-1′), 129.99 (C-2″, 6″), 129.05 (C-3″, 5″), 128.71 (C-2‴, 6‴), 127.87 (C-3‴, 5‴), 126.97 (C-5′), 126.83 (C-4‴), 125.49 (C-6′), 120.27 (C-4′), 113.77 (C-3′), 106.96 (C-5); ESI-MS: *m/z* 363 (M+Na, 35%), 341 (M+1, 85%). Anal. Calcd for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.94; H, 4.72; N, 8.26%.

Synthesis of 2-(6-([1,1′-biphenyl]-4-yl)-2-aminopyrimidin-4-yl)phenol, 3c′

The heterocycle **3c′** was synthesized through the condensation reaction of **1** (1.0 g, 0.003 mol) with guanidine hydrochloride (0.3 g, 0.003 mol) by applying the above demonstrated procedure.

3c′: Yield 0.85 (78%), yellow solid, m.p. 106-108°C. IR (KBr): 3412 (O-H), 3379, 3305 (N-H),

3044 (aromatic C-H), and 1592 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.81 (1H, brs, O*H*), 8.40 (2H, brs, NH_2), 7.90 (1H, s, H-5), 7.86 (2H, d, J_o = 7.5 Hz, H-2″, 6″), 7.76 (4H, m, H-3″, 5″, 2‴, 6‴), 7.46 (3H, m, H-3‴, 4‴, 5‴), 7.40 (1H, d, J_o = 7.1 Hz, H-5′), 7.33 (1H, dd, $J_{m,o}$ = 2.5, 7.7 Hz, H-6′), 6.96 (2H, d, J_o = 8.0 Hz, H-3′, 4′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.18 (C-2), 164.55 (C-4), 161.78 (C-6), 157.89 (C-2′), 144.27 (C-1″), 137.76 (C-4″, 1‴), 131.28 (C-1′), 130.39 (C-2″, 6″), 129.90 (C-3″, 5″), 128.58 (C-2‴, 6‴), 127.88 (C-3‴, 5‴), 127.15 (C-5′), 126.97 (C-4‴), 124.42 (C-6′), 118.51 (C-4′), 115.34 (C-3′), 108.05 (C-5); ESI-MS: *m/z* 340 (M+1, 16%), 339 (M^+, 100%) . Anal. Calcd for $C_{22}H_{17}N_3O$: C, 77.86; H, 5.05; N, 12.38. Found: C, 78.17; H, 5.07; N, 12.42%.

Synthesis of 2-(2-([1,1′-biphenyl]-4-yl)-1*H*-benzo [b][1,4]diazepin-4-yl)phenol, 4a″

A mixture of compound **1** (1.0 g, 0.003 mol), *o*-phenylenediamine (0.4 g, 0.003 mol), KOH (0.3 g, 0.006 mol) and absolute ethanol (25.0 mL) was refluxed vigorously for 8 h. Upon the completion of reaction, the excess solvent was distilled off under reduced pressure and residue mass was poured into crushed ice to afford a crude substance which was cyrstallized with EtOH to yield a pure benzodiazepine **4a″**.

4a″: Yield 0.95 (79%), brown solid, m.p. 128-130°C. IR (KBr): 3480 (N-H), 3214 (O-H), 3083 (aromatic C-H) and 1593 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.72 (1H, brs, O*H*), 8.71 (1H, brs, N*H*), 8.08 (4H, t, J_o = 8.1 Hz, H-3″, 5″, 2‴, 6‴), 7.93 (2H, d, J_o = 8.0 Hz, H-2″, 6″), 7.81 (2H, d, J_o = 8.2 Hz, H-3‴, 5‴), 7.76 (2H, dd, $J_{m,o}$ = 2.2, 7.9 Hz H-5′, 6′), 7.55 (1H, dd, $J_{p,o}$ = 1.0, 8.0 Hz H-10), 7.51 (2H, t, J_o = 8.4 Hz, H-8, 9), 7.41 (1H, t, J_o = 7.6 Hz, H-7), 7.16 (1H, dd, $J_{m,o}$ = 2.5, 7.8 Hz, H-4‴), 7.00 (1H, td, $J_{m,o}$ = 2.7, 8.0 Hz, H-4′), 6.58 (1H, d, J_o = 7.6 Hz, H-3′), 5.25 (IH, s, H-3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.15 (C-2), 155.73 (C-2′), 150.01 (C-6), 144.01 (C-11), 142.30 (C-4), 139.33 (C-1″), 135.69 (C-4″, 1‴), 135.14 (C-1′), 129.14 (C-2″, 6″), 129.02 (C-3″, 5″, 2‴, 6‴), 127.94 (C-3‴, 5‴), 127.61 (C-5′), 126.88 (C-4‴), 126.77 (C-8, 9), 120.81 (C-6′), 116.93 (C-7, 10), 116.12 (C-4′), 114.67 (C-3′), 90.37 (C-3); ESI-MS: *m/z* 411 (M+Na, 29%), 390 (M+2, 60%), 389 (M+1, 90%). Anal. Calcd for $C_{27}H_{20}N_2O$: C, 83.48; H, 5.19; N, 7.21. Found: C, 83.81; H, 5.16; N, 7.23%.

Synthesis of 2-(2-([1,1′-biphenyl]-4-yl)benzo[b] [1,4]oxazepin-4-yl)phenol, 4b″

The reaction of **1** (1.0 g, 0.003 mol) with 2-aminophenol (0.3 g, 0.003 mol) under the similar reactions conditions as explained above for **4a"** afforded the new product **4b″**.

4b″: Yield 0.96 g (74%), brown solid, m.p. 142-144°C. IR (KBr): 3268 (O-H), 3074 (aromatic C-H) and 1589 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.64 (1H, brs, O*H*), 8.01 (2H, d, J_o = 7.8 Hz, H-2″, 6″), 7.96 (4H, m, H-3″, 5″, 2‴, 6‴), 7.89 (3H, t, J_o = 7.3 Hz, H-3‴, 4‴, 5‴), 7.72 (1H, d, J_o = 8.0 Hz H-5′), 7.61 (2H, d, J_o = 7.4 Hz, H-8, 9), 7.55 (1H, td, $J_{m,o}$ = 2.1, 7.6 Hz, H-6′), 7.18 (2H, dd, $J_{m,o}$ = 2.6, 7.0 Hz, H-7, 10), 7.04 (1H, t, J_o = 8.2 Hz H-4′), 6.99 (1H, m, H-3′), 5.51 (IH, s, H-3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.68 (C-2), 157.75 (C-2′), 151.98 (C-6), 143.35 (C-11), 142.17 (C-4), 139.58 (C-1″), 136.41 (C-4″, 1‴), 134.72 (C-1′), 130.88 (C-2″, 6″), 129.95 (C-3″, 5″, 2‴, 6‴), 128.64 (C-3‴, 5‴), 127.33 (C-5′), 126.99 (C-4‴), 126.02 (C-8, 9), 119.21 (C-6′), 117.76 (C-7, 10), 116.54 (C-4′), 114.39 (C-3′), 93.74 (C-3); ESI-MS: *m/z* 390 (M+1, 90%), 389 (M^+, 32%). Anal. Calcd for $C_{27}H_{19}NO_2$: C, 83.27; H, 4.92; N, 3.60. Found: C, 83.60; H, 4.94; N, 3.58%.

Synthesis of 2-(2-([1,1′-biphenyl]-4-yl)benzo[b] [1,4]thiazepin-4-yl)phenol, 4c″

The heterocycle **4c″** was obtained by the reaction of **1** (1.0 g, 0.003 mol) and 2-aminothiophenol (0.4g, 0.003 mol) using the similar process as prescribed earlier for **4a″**.

4c″: Yield 0.89 g (68%), brown solid, m.p. 198-200°C. IR (KBr): 3257 (O-H), 3025 (aromatic C-H) and 1600 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.68 (1H, brs, O*H*), 8.16 (4H, d, J_o = 8.1 Hz, H-3″, 5″, 2‴, 6‴), 8.09 (2H, d, J_o = 8.0 Hz, H-2″, 6″), 7.91 (2H, d, J_o = 7.9 Hz, H-3‴, 5‴), 7.72 (2H, d, J_o = 8.1 Hz, H-8, 9), 7.65 (2H, d, J_o = 7.9 Hz, H-7, 10), 7.50 (3H, m, H-5′, 6′, 4‴), 7.39 (2H, t, J_o = 7.3 Hz, H-3′, 4′), 6.33 (IH, s, H-3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.35 (C-2), 158.61 (C-2′), 152.43 (C-6), 145.08 (C-11), 143.88 (C-4), 140.22 (C-1″), 136.50 (C-4″, 1‴), 135.26 (C-1′), 131.19 (C-2″, 6″), 130.66 (C-3″, 5″, 2‴, 6‴), 129.45 (C-3‴, 5‴), 128.76 (C-5′), 127.77 (C-4‴), 126.90 (C-8, 9), 122.19 (C-6′), 118.65 (C-7, 10), 117.32 (C-4′), 115.51 (C-3′), 99.15 (C-3); ESI-MS: *m/z* 407 (M+2, 65%), 406 (M+1, 13%), 405 (M^+, 88%). Anal. Calcd for $C_{27}H_{19}NOS$: C, 79.97; H, 4.72; N, 3.45. Found: C, 79.65; H, 4.74; N, 3.46%.

Synthesis of (*R*)-2-(5-([1,1′-biphenyl]-4-yl)-4,5-dihydroisoxazol-3-yl)phenol, 5

A solution of compound **1** (1.0 g, 0.003 mol), hydroxylamine hydrochloride (0.2 g, 0.003 mol), KOH (0.3 g, 0.006 mol) and dry EtOH (25.0 mL) was refluxed for 6 h. After the completion of reaction (inspected from TLC), the resulting mixture was added slowly into ice cold hydrochloric acid to acquire a solid product which were filtered off, washed with water and dried. The crude product was crystallized by using MeOH as a solvent to yield a pure product **5**.

5: Yield 0.74 g (70%), light brown solid, m.p. 154-156°C. IR (KBr): 3260 (O-H), 3073 (aromatic C-H), 2924 (aliphatic C-H) and 1600 cm^{-1} (C=N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (1H, brs, O*H*), 7.53 (4H, dd, $J_{m,o}$ = 2.8, 8.0 Hz, H-3″, 5″, 2‴, 6‴), 7.42 (3H, t, J_o = 7.2 Hz, H-3‴, 4‴, 5‴), 7.33 (4H, m, H-5′, 6′, 2″, 6″), 7.28 (1H, m, H-3′), 6.90 (1H, dt, $J_{m,o}$ = 2.1, 7.3 Hz, H-4′), 5.62 (1H, dd, J_{XA} = 4.6 Hz, J_{XM}= 11.5 Hz, H_X), 3.75 (1H, dd, J_{MX} = 11.5 Hz, J_{MA} = 17.2 Hz, H_M), 3.18 (1H, dd, J_{AX} = 4.6 Hz, J_{AM} = 17.2 Hz, H_A); ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.52 (C-2′), 154.25 (C-3), 141.56 (C-1″), 139.83 (C-4″), 139.17(C-1‴), 132.27 (C-1′), 129.87 (C-2″, 6″), 128.90 (C-3″, 5″)127.38 (C-2‴, 6‴), 127.00 (C-3‴, 5‴), 126.59 (C-5′), 126.09 (C-4‴), 117.81 (C-6′), 117.58 (C-4′), 112.74 (C-3′), 60.13 (C-5), 42.05 (C-4); ESI-MS: *m/z* 317 (M+2, 13%), 316 (M+1, 54%), 315 (M^+, 100%). Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 80.29; H, 5.45; N, 4.42%.

Conclusion

The present research work represents a general and efficient method for the synthesis of varied rings new heterocyclic products (pyrazolines, isoxazoline, pyrimidines and benzoazepines) under the very simple conditions without using any expensive and toxic reagents. One intermediate chalcone has been straightforwardly transformed into various heterocycles by using suitable cyclizing agents. Among the newly prepared heterocycles, pyrazolines and isoxazoline revealed the noticeable antimicrobial properties.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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